

DATA EVALUATION RECORD

NOA 446510 (MANDIPROPAMIDE)

Study Type: OPPTS 870.3100 [§82-1a], Subchronic Oral Toxicity Study in Mice

Work Assignment No. 4-1-121 A; formerly 3-1-121 A (MRIDs 46800213 and 46800217)

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NOA 446510 (MANDIPROPAMIDE)/036602

OPPTS 870.3100/ DACO 4.3.1/ OECD 408

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Template version 02/06

<p align="center">DATA EVALUATION RECORD</p>

STUDY TYPE: 90-Day Oral Toxicity [feeding]-mice; OPPTS 870.3100 § 82-1a] (rodent);
OECD 408.

PC CODE: 036602**DP BARCODE:** D328539**TXR#:** 0054273**TEST MATERIAL (PURITY):** NOA 446510 (Mandipropamide; 96.5% a.i.)**SYNONYMS:** 4-chloro-N-[2-[3-methoxy-4-(2-propynyloxy)phenyl]ethyl]-α-(2-propynyloxy)-benzeneacetamide

CITATION: Milburn, G. (2005) NOA446510: 90 day dietary toxicity study in the mouse. Central Toxicology Laboratory, Macclesfield, Cheshire, UK. Laboratory Study No: CTL/PM1265/Regulatory/Report; Syngenta No.: T004588-02, December 20, 2005. MRID 46800213. Unpublished.

Milburn, G. (2005) NOA446510: 28 day dietary range finding study in the mouse. Central Toxicology Laboratory, Macclesfield, Cheshire, UK. Laboratory Study No: CTL/KM1473/Regulatory/Report; Syngenta No.: T005180-01, December 20, 2005. MRID 46800217. Unpublished.

SPONSOR: Syngenta Crop Protection, Inc., 410 Swing Road, P.O. Box 18300, Greensboro, NC

EXECUTIVE SUMMARY - In a subchronic oral toxicity study (MRIDs 46800213 and 46800217), NOA 446510 (Mandipropamide; 96.5% a.i.; Batch No. SEZ2BP007) was administered in the diet to C57BL/10J;CD-1 mice (10/sex/dose) at dose levels of 0, 300, 800, 2000, or 5000 ppm (equivalent to 0/0, 37/47, 98/129, 248/316 and 624/800 mg/kg bw/day in males/females) for 90 days.

No adverse treatment-related effects were observed on mortality, clinical signs, food consumption, food utilization, hematology, or on gross pathology.

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In the 5000 ppm females, initial transient losses ($p \leq 0.01$) were observed in body weight gains on Days 2-3 contributing to a decreased ($p \leq 0.01$) overall (Weeks 1-14) body weight gain of 23%. Decreased ($p \leq 0.05$) body weight was noted on Days 2 and 3 (decr 1-2%) and at Week 14 (decr 4%).

In the 5000 ppm females ($n=10$), slight periportal eosinophilia was noted in 2 mice (and minimal eosinophilia in 7 mice) vs 0 controls. Adjusted liver weight increased by 31%. Together these findings were considered possibly indicative of slight hepatotoxicity.

The LOAEL is 5000 ppm (equivalent to 624/800 mg/kg/day in males/females), based on decreased body weight gain in males and females as well as the suggestion of effects on the liver (increased weights in males and females as well as microscopic pathology. The NOAEL is 2000 ppm (equivalent to 248/316 mg/kg/day in males/females).

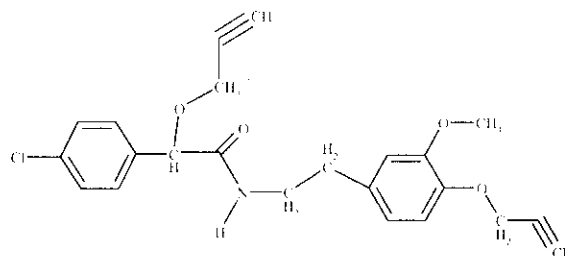
This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3100a; OECD 408) for a subchronic oral toxicity study in the mouse.

COMPLIANCE - Signed and dated Data Confidentiality, GLP Compliance, Flagging, and Quality Assurance statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

- 1. Test material:** NOA 446510
- Description:** Slightly beige solid
- Batch No.:** SEZ2BP007
- Purity:** 96.5% a.i.
- Compound stability:** Stable in the diet for up to 44 days at room temperature
- CAS # of TGAI:** 374726-62-2
- Structure:**



2. Vehicle and/or positive control: Diet

- 3. Test animals**
- Species:** Mouse
- Strain:** C57BL/10J_{CD-1}
- Age/weight at study initiation:** Approximately 34-38 days old; 18.9-24.4 g males; 17.3-20.5 g females
- Source:** Rodent Breeding Unit, Alderley Park (Cheshire, UK)
- Housing:** Housed in groups of up to 5 mice by common sex and dose in multiple racks
- Diet:** CT1 diet (Special Diets Services Ltd., Essex, UK), *ad libitum*
- Water:** Tap water, *ad libitum*
- Environmental conditions:**
- Temperature:** 22±3°C
- Humidity:** 30-70%
- Air changes:** ≥15 air changes/hour
- Photoperiod:** 12 hours light/12 hours dark
- Acclimation period:** At least 5 days

B. STUDY DESIGN

- 1. In life dates:** Start: June 18, 2002 End: Approximately September 18, 2002
- 2. Animal assignment:** Animals were randomly assigned to the test groups presented in Table 1.

TABLE 1: Study design ^a			
Test group	Dose to animal (ppm)	Dose to animal (mg/kg/day in M/F)	No. mice/sex
Control	0	0/0	10
Low	300	37.2/47.3	10
Mid-Low	800	98.0/128.9	10
Mid	2000	247.6/315.8	10
High	5000	624.3/800.5	10

^a Data were obtained from pages 21 and 24 of MRID 46800213.

3. **Dose-selection rationale:** Doses were selected on the basis of results from a concurrently submitted 28 day dietary toxicity study in the mouse (MRID 46800217), which is summarized in the Appendix to this DER.
4. **Treatment preparation, administration, and analysis:** Dietary formulations were prepared by triturating the appropriate amount of test substance in a premix to milled diet. The test diets were stored at room temperature for up to 44 days.

The stability of the test substance in the 100 and 10,000 ppm dietary formulations was tested for up to 44 days at room temperature in a separate study (MRID 46800216, concurrently submitted). The homogeneity (top, middle, bottom) of the test substance in the diet was tested at 300 and 5000 ppm prior to treatment. Concentrations at each dietary level were measured prior to the start of the study and on one occasion during the study.

Results

Homogeneity analysis (% CV): 0.2-1.7%

Stability analysis (% of nominal concentration): 101.4-103.5%

Concentration analysis (% of nominal concentration): 95.6-100.1%

The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the animals was acceptable.

- 5 **Statistics:** All data were evaluated using the MIXED procedure in SAS. Least-squares means for each group were calculated, and each group was compared to the control using a 2-sided Student's t-test, based on the error mean square in the analysis. Significance was indicated at 5 and 1% probability.

PARAMETER	ANALYSIS CONDUCTED
Body weight	Analysis of covariance (ANCOVA) on initial (Day 1) body weight
Food consumption, food utilization, and hematology	Analysis of variance (ANOVA)
Organ weights	ANOVA and ANCOVA on final body weight

Statistical analysis where n=2 (food consumption and food utilization) was not appropriate. Otherwise, if the assumptions for parametric testing were met, the statistical analyses were considered appropriate.

C. METHODS

1. Observations

- 1a. **Cageside observations:** Animals were observed twice daily for signs of toxicity and mortality.

- 1b. Clinical examinations:** Detailed clinical observations were performed prior to treatment, daily for Days 2-8, and weekly throughout the study.
- 1c. Neurological evaluations:** Neurological evaluation was not performed in this study. Subchronic (MRID 46800240) and acute (MRID 46800242 and 46800241) neurotoxicity studies in rats were concurrently submitted.
- 2. Body weight:** All animals were weighed prior to treatment, daily for Days 2-8, weekly throughout the study, and at necropsy. Cumulative body weight gain was calculated each time the animals were weighed beginning at Day 2.
- 3. Food consumption, food utilization, and compound intake:** Mean food consumption (g food/animal/day) was determined weekly for each cage (n=2). Food utilization was calculated as the bodyweight gained by the mice in the cage per 100 g of food eaten for Weeks 1-4, 5-8, 9-13, and Overall (Weeks 1-13). Test substance intakes (mg/kg body weight/day) were calculated as time-weighted averages from the food consumption, nominal test compound concentration, and body weight data.
- 4. Ophthalmoscopic examination:** Eyes were not examined.
- 5. Hematology and clinical chemistry:** Blood was collected from all animals at termination by cardiac puncture. The CHECKED (X) parameters were examined for hematology, but clinical chemistry was not performed.

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpuscular HGB concentration (MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpuscular volume (MCV)*
X	Platelet count*		Reticulocyte count (RET)
	Blood clotting measurements*	X	Red blood cell distribution width
	(Activated partial thromboplastin time)	X	Blood films analyzed when necessary
	(Clotting time)		
	(Prothrombin time)		

* Recommended for 90-day oral rodent studies based on Guideline 870.3100

- 6. Urinalysis:** Urinalysis was not performed, but is optional based on Guideline 870.3100.

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7. **Sacrifice and pathology:** All mice were killed on Day 92 by exsanguination under halothane Ph. Eur. Anesthesia (fed/fasted not indicated). All animals were necropsied. The following CHECKED (X) tissues were collected. Additionally, the (XX) organs from all mice sacrificed on schedule were weighed (paired organs weighed together).

DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC	
	Tongue	X	Aorta*	XX	Brain*+
X	Salivary glands*	XX	Heart*+	X	Peripheral nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	XX	Spleen*+	X	Eyes*
X	Jejunum*	X	Thymus*+		
X	Ileum*				
X	Cecum*				
X	Colon*				
X	Rectum*				
XX	Liver*+				
X	Gall bladder (not rat)*				
	Bile duct (rat)				
X	Pancreas*				
RESPIRATORY		UROGENITAL		GLANDULAR	
X	Trachea*	XX	Kidneys*+	XX	Adrenal gland*+
X	Lung*	X	Urinary bladder*		Lacrimal gland
X	Nose*	XX	Testes*+	X	Parathyroid*
X	Pharynx*	XX	Epididymides*+	X	Thyroid*
X	Larynx*	X	Prostate*		
		X	Seminal vesicles*		
		XX	Ovaries*+		
		XX	Uterus*+ (including cervix)		
		X	Mammary gland* (female only)		
		X	Vagina		
		X	Oviduct		
		X	Preputial gland		
				OTHER	
				X	Bone (femur and sternum)
				X	Skeletal muscle
				X	Skin*
				X	Joint
				X	All gross lesions and masses*

* Recommended for 90-day oral rodent studies based on Guideline 870.3100

+ Organ weights required for rodent studies.

The Sponsor stated that each tissue was fixed in an appropriate fixative. All tissues were processed routinely and stained with hematoxylin and eosin. All tissues from the control and 5000 ppm groups were examined microscopically. Additionally, liver samples from all dose groups were also examined.

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I. RESULTS

A. OBSERVATIONS

1. **Mortality:** No unscheduled deaths occurred.
2. **Observations:** No treatment-related clinical signs were observed.

- B. BODY WEIGHT AND BODY WEIGHT GAIN:** All differences ($p \leq 0.05$) in body weight in the treated groups compared to controls were minor and/or unrelated to dose. Decreased ($p \leq 0.01$) overall (Weeks 1-14) body weight gain was noted in the 5000 ppm males ($\downarrow 21\%$) and females ($\downarrow 23\%$).

TABLE 2. Average body weights (\pm SD) and body weight gains in mice treated with NOA 446510 for up to 14 weeks ^a					
Study Week	Dose (ppm)				
	0	300	800	2000	5000
Males					
1 (day 1)	22.1 \pm 1.5	22.7 \pm 1.1	22.4 \pm 1.2	22.5 \pm 1.0	22.5 \pm 1.1
7	27.9 \pm 2.2	26.8 \pm 0.9** ($\downarrow 4$)	27.6 \pm 1.2	27.3 \pm 2.0	27.1 \pm 1.2
14	32.0 \pm 2.8	29.9 \pm 0.8** ($\downarrow 7$)	31.0 \pm 1.4	30.5 \pm 2.0* ($\downarrow 5$)	30.2 \pm 1.3** ($\downarrow 6$)
BWG (Days 1-2)	0.3 \pm 0.4	0.3 \pm 0.4	0.4 \pm 0.4	0.4 \pm 0.3	-0.2 \pm 0.2** (N/A)
BWG (Days 1-3)	0.7 \pm 0.4	0.5 \pm 0.6	0.5 \pm 0.3	0.6 \pm 0.3	0.6 \pm 0.3
BWG (Weeks 1-7)	5.8 \pm 1.3	4.1 \pm 0.9** ($\downarrow 29$)	5.2 \pm 1.1	4.8 \pm 1.9	4.6 \pm 1.2* ($\downarrow 21$)
BWG (Weeks 1-14)	9.8 \pm 1.9	7.2 \pm 0.7** ($\downarrow 27$)	8.6 \pm 1.1	8.1 \pm 1.8* ($\downarrow 17$)	7.7 \pm 1.5** ($\downarrow 21$)
Females					
1(day 1)	18.3 \pm 0.7	18.9 \pm 0.8	18.7 \pm 0.8	18.7 \pm 0.9	18.7 \pm 0.7
7	21.4 \pm 1.1	22.1 \pm 1.2	21.5 \pm 0.9	21.1 \pm 0.8	21.5 \pm 0.9
14	24.4 \pm 1.3	25.0 \pm 1.0	24.5 \pm 0.9	24.4 \pm 1.3	23.4 \pm 0.8** ($\downarrow 4$)
BWG (Days 1-2)	0.1 \pm 0.7	-0.0 \pm 0.6	-0.2 \pm 0.5	-0.4 \pm 0.6** (N/A)	-0.5 \pm 0.4** (N/A)
BWG (Days 1-3)	0.4 \pm 0.9	-0.1 \pm 0.8* (N/A)	0.3 \pm 0.8	-0.4 \pm 0.6** (N/A)	-0.2 \pm 0.4** (N/A)
BWG (Weeks 1-7)	3.1 \pm 1.2	3.2 \pm 0.9	2.8 \pm 1.0	2.4 \pm 0.7	2.8 \pm 0.5
BWG (Weeks 1-14)	6.1 \pm 1.1	6.1 \pm 0.5	5.8 \pm 1.2	5.7 \pm 1.3	4.7 \pm 0.5** ($\downarrow 23$)

a Data (n=10) were obtained from Tables 4-5 on pages 36-49 of MRID 46800213. Percent difference from controls, calculated by the reviewers, is included in parentheses. Analysis of covariance (ANCOVA) on initial (Week 1) bodyweight was performed by Sponsor to determine significant differences; adjusted means are not presented in this table.

* Significantly different from controls; $p \leq 0.05$

** Significantly different from controls; $p \leq 0.01$

N/A Not applicable

C. FOOD CONSUMPTION AND COMPOUND INTAKE

1. **Food consumption and utilization:** No treatment-related effect was observed on food consumption or utilization. During Week 13, decreased ($p \leq 0.05$) food consumption was noted in the 5000 ppm females ($\downarrow 16\%$). This was considered an incidental response because all other values in the treated female groups were similar to controls throughout treatment. Differences ($p \leq 0.05$) from the control group in males were minor and/or unrelated to dose. Differences ($p \leq 0.05$) in food utilization were only observed in the males, and these differences were unrelated to dose.

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2. **Compound consumption:** Compound intake values (mg/kg/day) are presented in Table 1 of this DER.

D. **HEMATOLOGY:** No treatment-related effect was observed on hematology. All differences ($p \leq 0.05$) were minor (2-5%), such as decreases in hemoglobin, hematocrit, mean corpuscular volume, and mean corpuscular hemoglobin; and increases in red cell distribution width.

E. SACRIFICE AND PATHOLOGY

1. **Organ weight:** Terminal body weights in the treated groups were similar to controls (Table 3). Absolute and adjusted for terminal body weight liver weights were increased ($p \leq 0.01$) by 15-38% in both sexes at 2000 and 5000 ppm. Additionally, adjusted liver weights were increased ($p \leq 0.05$) by 9% in both sexes at 800 ppm

TABLE 3. Mean (\pm SD) liver weights in mice treated with NOA 446510 for 14 weeks ^a					
Parameter	Dose (ppm)				
	0	300	800	2000	5000
Males					
Terminal body weight (g)	32.0 \pm 2.8	29.9 \pm 0.8	31.0 \pm 1.4	30.5 \pm 2.0	30.2 \pm 1.3
Liver absolute (g)	1.35 \pm 0.15	1.29 \pm 0.08	1.40 \pm 0.13	1.55 \pm 0.17** (\uparrow 15)	1.71 \pm 0.19** (\uparrow 27)
relative to BW (%)	4.22 \pm 0.21	4.32 \pm 0.23	4.51 \pm 0.25	5.07 \pm 0.35	5.66 \pm 0.41
adjusted for BW (g)	1.27	1.34	1.38* (\uparrow 9)	1.56** (\uparrow 23)	1.75** (\uparrow 38)
Females					
Terminal body weight (g)	24.4 \pm 1.3	25.0 \pm 1.0	24.5 \pm 0.9	24.4 \pm 1.3	23.4 \pm 0.8
Liver absolute (g)	1.04 \pm 0.10	1.09 \pm 0.08	1.15 \pm 0.15	1.21 \pm 0.14** (\uparrow 16)	1.28 \pm 0.10** (\uparrow 23)
relative to BW (%)	4.27 \pm 0.26	4.36 \pm 0.26	4.67 \pm 0.48	4.95 \pm 0.44	5.47 \pm 0.31
adjusted for BW (g)	1.04	1.03	1.13* (\uparrow 9)	1.20** (\uparrow 15)	1.36** (\uparrow 31)

a Data were obtained from Table 9 on page 65 of MRID 46800213. Percent difference from controls, calculated by the reviewers, is included in parentheses.

* Significantly different from controls; $p \leq 0.05$

** Significantly different from controls; $p \leq 0.01$

2. **Gross pathology:** No treatment-related effect was noted on gross pathology.

3. **Microscopic pathology:** Increased periportal eosinophilia in the liver was noted in the 5000 ppm males (5/10; minimal severity) and the ≥ 2000 ppm females (8-9/10; minimal to slight severity) vs 0/10 in the controls and other dose groups (Table 4).

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TABLE 4. Incidence (# affected/10) of eosinophilia in the liver of mice treated with NOA 446510 for 14 weeks ^a					
Parameter	Dose (ppm)				
	0	300	800	2000	5000
Males					
Liver periportal eosinophilia (Total), Minimal	0	0	0	0	5
Females					
Liver periportal eosinophilia (Total)	0	0	0	8	9
Minimal	0	0	0	7	7
Slight	0	0	0	1	2

a Data were from Table 11 on pages 74 and 77 of MRID 46800213.

III. DISCUSSION AND CONCLUSIONS

- A. INVESTIGATOR'S CONCLUSIONS:** The Sponsor stated that at 2000 and 5000 ppm the following findings were noted: decreased bodyweights, decreases in a number of red cell parameters, hepatocyte periportal eosinophilia, and increased liver weights in both sexes. Spleen weights were decreased in females only.
- B. REVIEWER'S COMMENTS:** No adverse treatment-related effects were observed on mortality, clinical signs, food consumption, food utilization, hematology, or on gross pathology.

In the 5000 ppm females, initial transient losses ($p \leq 0.01$) were observed in body weight gains on Days 2-3 contributing to a decreased ($p \leq 0.01$) overall (Weeks 1-14) body weight gain of 23%. Decreased ($p \leq 0.05$) body weight was noted on Days 2 and 3 ($\downarrow 1-2\%$) and at Week 14 ($\downarrow 4\%$).

All differences ($p \leq 0.05$) in body weight in the treated male groups compared to controls were minor and/or unrelated to dose. Initial transient losses ($p \leq 0.01$) were observed in body weight gains on Day 2 in the 5000 ppm males. Body weight gains in 5000 ppm males over the 14-week study were reduced 21%. Consequently, treatment-related effects on body weight gain was observed in the 5000 ppm males and females.

Absolute and adjusted for terminal body weight liver weights were increased ($p \leq 0.01$) by 15-38% in both sexes at 2000 and 5000 ppm. Additionally, adjusted liver weights were increased ($p \leq 0.05$) by 9% in both sexes at 800 ppm; this minor effect was not adverse. Increased periportal eosinophilia in the liver was noted in the 5000 ppm males (5/10; minimal severity) and the ≥ 2000 ppm females (8-9/10; minimal to slight severity) vs 0/10 in the controls and other dose groups.

In the 5000 ppm females (n=10), slight periportal eosinophilia was noted in 2 mice (and minimal eosinophilia in 7 mice) vs 0 controls. Adjusted liver weight increased by 31%. Together these findings were considered possibly indicative of slight hepatotoxicity. In the 5000 ppm males (n=10) only minimal periportal eosinophilia was noted in 5 mice vs 0 controls, which was not considered an adverse finding due to lack of severity. Without corroborating evidence of hepatotoxicity in the 5000 ppm males, the increase in adjusted liver weight of 38% was also not considered adverse. At 2000 ppm, only 1 female was noted with slight eosinophilia (and minimal eosinophilia in 7 mice) and the increase in adjusted liver weight for the 2000 ppm females was only 15%. These changes were not considered adverse.

No treatment-related effect was observed on hematology. Although the Sponsor stated that there were decreases in a number of red cell parameters, all differences ($p \leq 0.05$) were minor (2-5%), such as decreases in hemoglobin, hematocrit, mean corpuscular volume, and mean corpuscular hemoglobin; and increases in red cell distribution width.

The LOAEL is 5000 ppm (equivalent to 624/800 mg/kg/day in males/females), based on decreased body weight gain in males and females as well as the suggestion of effects on the liver (increased weights in males and females as well as microscopic pathology). The NOAEL is 2000 ppm (equivalent to 248/316 mg/kg/day in males/females).

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3100a; OECD 408) for a subchronic oral toxicity study in the mouse.

C. STUDY DEFICIENCIES: The following minor deficiencies were noted but do not change the conclusions of the reviewer:

- \$ Clinical chemistry was not performed.
- \$ Ophthalmoscopic examinations were not performed.
- \$ Blood clotting measurements were not conducted.
- \$ The thymus was not weighed.
- \$ Statistical analysis where n=2 (food consumption and food utilization) was not appropriate.

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Appendix

In a 28-day oral toxicity study (MRID 46800217), NOA 446510 (Mandipropamide; 98.5% a.i.; Batch No. KI-6380/6) was administered to 5 C57BL/10J,CD-1 mice/sex/dose in the diet at dose levels of 0, 700, 2100, or 7000 ppm (equivalent to 0/0, 108/122, 319/378, and 1411/1350 mg/kg/day in males/females) for 28 days. Additionally 12 mice/sex/dose were similarly treated, and 3 mice/sex/dose were sacrificed and cardiac blood samples collected on Days 2, 3, 4, and 29. The plasma was analyzed for the test substance; however, it was determined that the time of sampling was inappropriate for the characterization of test substance kinetics, and the data were not reported.

No adverse, treatment-related effects were observed on mortality, clinical signs, food consumption, hematology, clinical signs, clinical chemistry, or gross pathology.

The following findings were noted: (i) decreased ($p \leq 0.05$) bodyweights in the 7000 ppm males and females throughout the study ($\downarrow 7$ -13%), and in the 2100 ppm females on Days 2, 3, 6, 15, 22, and 29 ($\downarrow 3$ -9%); (ii) body weight loss in the 7000 ppm males and females through Day 8 and in the 2100 ppm females on Days 2, 3, and 6; (iii) decreased ($p \leq 0.05$) body weight gains throughout the study in the 7000 ppm males ($\downarrow 56$ -667%) and in the 2100 and 7000 ppm females ($\downarrow 50$ -450%; not statistically significant at 2100 ppm on Day 7); (iv) decreased ($p \leq 0.05$) bodyweight gains in the 700 ppm females at Day 29 ($\downarrow 23$ %); (v) increased ($p \leq 0.01$) adjusted (for terminal body weight) liver weights in the 2100 and 7000 ppm females ($\uparrow 23$ -53%); and (vi) increased incidence of minimal to slight increase eosinophilia and hypertrophy in periportal hepatocytes in the 7000 ppm females (5/5 treated vs 0/5 controls). The effect on bodyweight gains in the 700 ppm was considered not adverse in the absence of corroborating evidence of toxicity and because terminal body weights were only decreased by 1% in this group. The increased weight in the liver of 2100 ppm females was considered not adverse in the absence of corroborating evidence of hepatotoxicity at that dose level.

The LOAEL was 2100 ppm (319/378 mg/kg/day in males/females) based on decreased body weights and body weight gains in the females. The NOAEL is 700 ppm (equivalent to 108/122 mg/kg/day in males/females).

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